Monatshefte für Chemie 131, 1161–1165 (2000)

Monatshefte für Chemie
Chemical Monthly

Corrected Structure of Aglalactone Isolated from *Aglaia elaeagnoidea* (Meliaceae)

Christoph Seger[1,*], **Otmar Hofer**[1], and **Harald Greger**[2]

[1] Institute of Organic Chemistry, University of Vienna, A-1090 Wien, Austria
[2] Comparative Phytochemistry Department, Institute of Botany, University of Vienna, A-1030 Wien, Austria

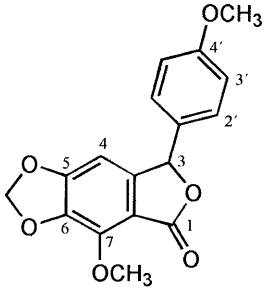
Summary. The structure of aglalactone, a dihydrobenzofuranone from *Aglaia elaeagnoidea*, was revised on the basis of 2D NMR data and lanthanide induced shifts (LIS).

Keywords. Dihydrobenzofuranone; *Aglaia*; Meliaceae

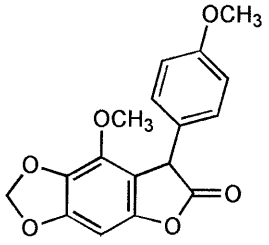
Introduction

In our recent screening for biologically active compounds in the genus *Aglaia* (Meliaceae) we have isolated a series of cyclopenta[*b*]benzofurans together with a presumably related lactone as a minor constituent [1]. Both the cyclopenta[*b*]benzofurans (named pannellins) and the lactone (named aglalactone) showed a similar substitution pattern of a benzofuran system, hence suggesting biogenetic connections. Aglalactone (corrected structure **1**, originally published incorrect structure **2**) and pannellin (**3**) are characterized by aromatic methoxy-methylenedioxy substituents in a 1,2,3-arrangement and a *p*-methoxyphenyl substituent at the five-membered ring. The cyclopenta[*b*]benzofurans belong to the group of flavaglines which are supposed to be derived biosynthetically from cinnamic acid and flavanoids [1–3]. The flavanoid origin is the reason for the general 1,3,5-oxygenation pattern of the A-ring of flavaglins which correlates to a phloroglucinol-derived aromatic system. Since ^{1}H and ^{13}C NMR data of aglalactone matched fairly well with those of pannellin (5-H: $\delta = 6.31$ ppm in **2**, 6.32 ppm in **3**; a reasonably good correlation of the ^{13}C NMR data for supposedly equivalent positions in **2** and **3** [1]), we originally proposed an analoguous benzene 1,2,3,5-oxygenation pattern for both compounds (structures **2** and **3**). However, we later recognized that the ^{13}C NMR resonance of C-3 (which has no equivalent position in flavagline **3**) deviated from the value which should be expected for the originally proposed structure **2**. This discrepancy prompted us to reinvestigate the structure of the title compound.

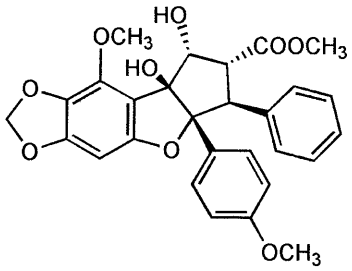
* Corresponding author



1 (aglalactone)



2



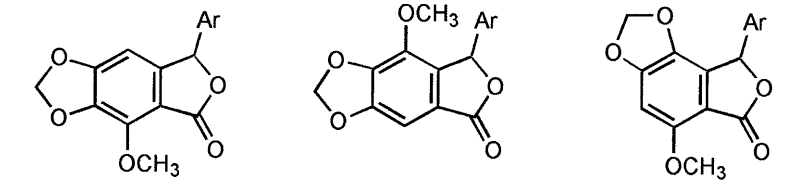
3 (pannellin)

Results and Discussion

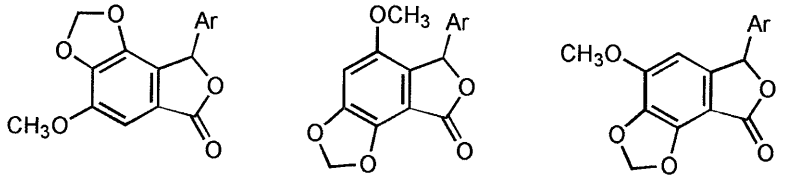
A ^{13}C chemical shift of $\delta = 81.0$ ppm seems very high for the C-3 resonance in the originally published structure **2**, even if this CH group is located in an α-position to a carbonyl group and suffers the influence of two aromatic systems (twofold benzylic position). The chemical shift value of a methine group like that should not be higher than *ca.* 60 ppm which is *e.g.* supported by a value of $\delta = 50.6$ ppm for a similar 3-phenyl-2,3-dihydrobenzo[*b*]furan-2-one [4]. The value of 81.0 ppm for C-3 implies that the lactonic oxygen atom should be next to this methine carbon. This results in an exchange of O and CO in the incorrect benzofuranone structure **2**, giving a –CO–O–CHPh– sequence of a lactonic 3*H*-isobenzofuranone as in structure **1**. A ketonic sequence –O–CHPh–CO– can be excluded because the ^{13}C shift value of 167.9 ppm is clearly in favour of a lactone and not a ketone [1]. In the revised structure of aglalactone, the biosynthetically expected phloroglucine-type oxygenation of the aromatic system had to be discarded. However, ^{13}C NMR data from the literature strongly support the 3*H*-isobenzofuranone (1,3-dihydrobenzo[*c*]furan-1-one) structure of the five-membered ring: in two relevant 3-phenylisobenzofuranones, δ(C-3) amounts to 81.2 [5] and 82.7 ppm [6], respectively. Comparison of the ^{1}H NMR data of the CHPh methine proton again supports the 3*H*-isobenzofuranone structure: the experimental value of 6.11 ppm for aglalactone agrees well with the values of 6.12 [5] and 6.3–6.4 ppm [6] for related 3-phenylisobenzofuranones and not at all with the value of 4.98 ppm for a 3-phenylbenzofuranone related to the incorrect structure **2** [4].

The 3*H*-isobenzofuranone structure contains three oxygen substituents at the aromatic ring. Two linear (**I**, **II**) and four angular structures (**III**–**VI**) are in principle possible arranging the methylenedioxy and the methoxy group in different ways at the isobenzofuranone unit. LIS (lanthanide induced shift) measurements and long-range heteronuclear shift correlation data were mainly used to prove structure **I** ($\equiv$ **1**) for aglalactone.

NOE data were of little help for our purposes because only correlations within the *p*-methoxyphenyl substituent were detectable in a NOESY experiment (see Experimental). No NOE was observed between the methoxy group and the aromatic proton of the isobenzofuranone system. This implies that the angular structures **III**–**VI** are most unlikely, because aromatic *o*-OMe$\rightarrow$H effects are usually rather strong due to the planar conformation of the aromatic methoxy group [7] which should



I **II** **III**



IV **V** **VI**

point towards the sterically less hindered aromatic C–H unit in all angular structures **III–VI**. However, the absence of NOE contacts cannot be used as a reliable argument.

On the other hand, measurement of the LIS values gave a clear-cut proof that the methoxy group is positioned at C-7 and that the carbonyl oxygen is attached to C-1, which is only compatible with the 3*H*-isobenzofuranone structures **I** and **III**. Complexation with Eu(*fod*)$_3$ gave a rather high shift value for the methoxy group attached to the isobenzofuranone moiety (see Table 1). This proves immediately that the complexation is bidentate, because single methoxy groups exhibit very weak coordinating properties [8]. Only in a bidentate complexation the coordination of the methoxy oxygen takes place easily, leading to high LIS values of the methoxy groups involved [8–10]. Since the LIS value of the methylenedioxy group shows no special enhancement, the only reasonable explanation for the strong complexation of aglalactone is the assumption of a bidentate complex between the C-1 carbonyl group and the 7-methoxy function. A bidentate complexation between the methylenedioxy moiety and a neighbouring methoxy group can be excluded because this type of complexation with shift reagents is usually very weak [11] and should be indicated by higher LIS values for the OCH_2O protons. In contrast, a carbonyl group is a well coordinating function and represents a much better partner for any bidentate complexation. Other bidentate complexes have been observed previously for different oxygen-containing functionalities [10–13]. Only structures **I** and **III** are compatible with bidentate coordination. Model calculations of the LIS values [9, 12] for a bidentate complex of **I** (identical with structure **1**) gave a good fit with 3.5% average deviation between experimental and calculated values (see Table 1), whereas structure **III** did not allow a fit better than 30%.

The same structure **1** can be derived from long-range shift correlation (HMBC) data. A weak cross peak from C-1 (carbonyl) to 3-H is compatible with the sequence –CHAr–O–CO–, and a very strong cross peak C-4→3-H complemented by its

Table 1. NMR data of aglalactone (**1**)[a]

No.	$\delta(^1H)$/ ppm	mult.	*J*/Hz	^1H LIS exp. (calc.)[b]	$\delta(^{13}C)$/ ppm	mult.	HMBC (C→H)[c]
1					167.9	s	(3)
3	6.11	brs		0.55 (0.54)	81.0	d	4, 2′/6′
3a					148.0	s	3
4	6.31	d	0.5	0.46 (0.45)	96.9	d	3
5					155.6	s	4, OCH_2O (3)
6					136.0	s	4, OCH_2O
7					141.6	s	7-OCH_3 (4)
7a					110.3	s	4 (3)
1′					128.6	s	3, 3′/5′ (2′/6′)[d]
2′/6′	7.17	m		0.16 (0.16)	128.5	d	3, 3′/5′ (6′/2′)[d]
3′/5′	6.88	m		0.00 (−0.01)	114.3	d	2′/6′, 5′/3′
4′					160.3	s	2′/6′, 3′/5′, 4′-OCH_3
OCH_2O[e]	6.05	d	1.1	0.39 (0.38)	102.3	t	
	6.03	d	1.1	0.39 (0.38)			
7-OCH_3	4.23	s		2.34 (−)	60.6	q	
4′-OCH_3	3.80	s		−0.01 (−0.02)	55.3	q	

[a] All data in $CDCl_3$; [b] LIS values in ppm, extrapolated to a concentration ratio of **1**:Eu(*fod*)$_3$ = 1:1; [c] weak cross peaks in parentheses; [d] C-1′ and C-2′/6′ cannot be distinguished; [e] diastereotopic methylene group

counterpart C-3→4-H proves clearly that the remaining aromatic proton of the isobenzofuranone unit is located *ortho* relative to the ring fusion position C-3a. This supports again structure **I** in comparison with the non-compatible structure **III**. Further evidence is furnished by the ^1H NMR spectra showing a coupling constant of 0.5 Hz between the aromatic resonance 4-H and the methine resonance 3-H. Strong HMBC cross peaks C-5→4-H and C-6→4-H and a very weak cross peak C-7→4-H support again position 7 for the methoxy group of the benzofuranone system. Further characteristic cross peaks allowed the assignment of all ^1H and ^{13}C NMR resonances (Table 1).

Experimental

The NMR experiments were obtained on a wide-bore Bruker DRX 400 instrument equipped with either a tunable broad band inverse probe tuned to ^{13}C (for gradient selected 2D experiments) or a dual $^1H/^{13}C$ probe for the 1D experiments. The sample concentration was 1.7 mg/0.7 cm^3 $CDCl_3$, and the sample temperature was 300 K. The spectra were referenced to internal *TMS* (^1H, 0.00 ppm) and to the $CDCl_3$ solvent signal (^{13}C, 77.00 ppm). All experiments were performed with standard pulse programs provided by the spectrometer manufacturer. The HMBC experiment was optimized for a long-range coupling constant of 8 Hz. The lanthanide induced shifts (LIS) were determined by adding increasing amounts of Eu(*fod*)$_3$ (Merck) to a solution of *ca.* 1 mg of substrate in 0.5 cm^3 $CDCl_3$ and extrapolation to a ratio substrate:reagent = 1:1. For the calculation of the LIS values of bidentate complexes, a modified version of the computer program PDIGM was used [9, 13].

7-Methoxy-3-(4-methoxyphenyl)-5,6-methylenedioxy-1,3-dihydrobenzo[c]furan-1-one
(**1**, *aglalactone*)

^{1}H NMR, ^{13}C NMR, ^{1}H LIS, and HMBC data are listed Table 1; NOESY (H→H): 3 → 2′/6′, 2′/6′ → 3 and 3′/5′, 3′/5′ → 2′/6′ and 4′-OCH_3, 4′-OCH_3 →; 3′/5′; for other spectroscopic data, see Ref. [1].

Acknowledgements

The authors are indebted to Mag. *Thomas Pacher* for the isolation of a new batch of the analyte. The investigation was supported by the Austrian National Commitee for the Intergovernmental Programme ''Man and Biosphere'' and by the *Fonds zur Förderung der wissenschaftlichen Forschung in Österreich* (project No. 12385-CHE).

References

[1] Brader G, Vajrodaya S, Greger H, Bacher M, Kalchhauser H, Hofer O (1998) J Nat Prod **61**: 1182
[2] Bacher M, Hofer O, Brader G, Vajrodaya S, Greger H (1999) Phytochemistry **52**: 253
[3] Nugroho BW, Edrada RA, Wray V, Witte L, Bringmann G, Gehling M, Proksch P (1999) Phytochemistry **51**: 367
[4] Moody CJ, Doyle KJ, Elliott MC, Mowlem TJ (1997) J Chem Soc Perkin Trans I, 2413
[5] Falk H, Mayr E (1995) Monatsh Chem **126**: 699
[6] Al-Hamdany R, Al-Rawi JM, Ibrahim S (1987) J Prakt Chem **329**: 126
[7] Hofer O (1978) Monatsh Chem **109**: 406
[8] Wright GE, Wei TY (1973) Tetrahedron **29**: 3775
[9] Hofer O (1986) J Chem Soc Perkin Trans II, 715
[10] Hofer O (1976) In: Topics in Stereochemistry, Vol **9**: 111–197 (Allinger NL, Eliel El (eds))
[11] Hofer O, Wurz G (1992) Monatsh Chem **123**: 105
[12] Schüttler R, Hoffmann RW (1973) Tetrahedron Lett 5109
[13] Hofer O, Griengl H, Nowak P (1978) Monatsh Chem **109**: 21

Received June 29, 2000. Accepted July 11, 2000